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Via Federal Express

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Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20004



Dear 8(e) Coordinator:

8EHQ-12-18664A

Generic Name: Dioxypyrimidium inner salt

This letter is to inform you of the results of acute oral and reproductive toxicity studies with the above referenced R&D test substance. To the best of our knowledge, this substance is not on the TSCA inventory.

Acute Oral in Mice

Test substance formulated in 0.5% methylcellulose in 0.1% Tween-80 was administered by oral gavage to 5 fasted male and 5 fasted female mice at a dose of 5000 mg/kg. The mice were observed for mortality, body weight effects, and clinical signs for up to 14 days after dosing. The surviving mice were sacrificed and given a complete gross pathology examination to detect any grossly observable evidence of organ or tissue damage. Clinical signs were observed in all mice and included eyelid ptosis, spasm, yellow-stained bedding, ataxia, cold to touch, low posture, and/or splayed limbs. All clinical signs resolved by test day 3. Gross findings observed were lungs discoloration and stomach ulcer erosion in one animal that was found dead. The oral LD50 was greater than 5000 mg/kg in male and female mice.

Reproductive

In this reproductive toxicity study, dietary concentrations of 0, 400, 1500, and 6000 ppm were administered to groups of 10 Crl:CD(SD) rats per sex per concentration. Dietary concentrations were reduced to 60% of initial concentrations during lactation and for the first three weeks following weaning for F1 males and females that were designated for evaluation through postnatal day (PND) 60. The period of administration for P1 males and females included the 28-day prematuring period, cohabitation, gestation, lactation, and for F1 offspring, through onset of puberty at PND 60. P1 males were exposed for 67 days. P1 females were exposed until weaning of litters on PND 21. F1 offspring were potentially exposed via gestation and lactation, and weanlings were administered test diets from PND 21-60. At 6000 ppm, significant reductions in body weight and food consumption parameters were noted for P1 and F1 males and females. Decreased mean litter size at birth due to significantly fewer implantation sites and decreased pup weight at birth and during lactation were observed at 6000 ppm compared to control. The time to preputial separation in F1 males was slightly delayed; the mean day of achievement was 49.0 compared with 43.9 in controls. The relevant historical control data mean is 43.2 and ranges from 39.9 to 48.8 days. A delay in achievement of preputial separation has been demonstrated to correlate with and may be secondary to reductions in body weight. Therefore, this apparent delay in pubertal onset is considered secondary to the marked body weight effects at this dietary concentration. Liver weight parameters were increased in all treated male groups and in the 6000 ppm female groups, and were associated with microscopic centrilobular hepatocellular hypertrophy. Also observed microscopically in the liver of 6000 ppm P1 males was minimal vacuolation of periportal hepatocytes, possibly due to mobilization of fat stores due to reduced food consumption. Increased thyroid weight parameters in the 6000 ppm male group were not associated with correlative histological changes. Decrease in absolute weights of epididymides, seminal vesicles, and ovaries and equivocally greater severity of mucification of vaginal epithelium, a normal finding in lactating animals, at 6000 ppm compared to control was attributed to the significant reduction in the body weight in this

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group. In the F1 generation, organ weight changes included brain, spleen, and thymus in F1 weanlings and adrenal, brain, epididymides, liver, kidney, prostate, seminal vesicles, and ovaries in F1 adults at 6000 ppm. Minimal atrophy of epididymal tubules secondary to body weight decrements was noted in F1 rats at 6000 ppm.

Acute Neurotoxicity in Rats

Young adult male and female Crl:CD(SD) rats (12 rats /sex/dose) were administered a single oral dose by gavage of 0, 100, 500, or 2000 mg/kg body weight of test substance in 0.1% Tween-80 in 0.5% methylcellulose. The rats were weighed on test days 0, 1, 7, and 14. Food consumption was determined for the intervals of test days 0-1, 0-7, 7-14, and 0-14. Clinical signs of toxicity were assessed daily from test day 0 through the day of sacrifice. A neurobehavioral test battery, consisting of motor activity and functional observational battery assessments, was conducted on all study rats prior to test substance administration, and on test days 0, 7, and 14. On test day 16, six rats per sex per group were anesthetized and underwent whole-body in situ perfusion. Tissues from the control and 2000 mg/kg groups and gross lesions were processed for histopathology and examined. Statistically significant reductions in body weight and food consumption parameters were noted at 500 and 2000 mg/kg. A statistically significant increase compared to control in forelimb grip strength was observed on test day 0 in females administered 2000 mg/kg and on test day 7 in females administered 500 mg/kg. A statistically significant reduction compared to control in forelimb grip strength was observed on test day 14 in males administered 2000 mg/kg. No test substance-related or statistically significant effects occurred on hindlimb grip strength or hindlimb footsplay for either males or females administered any dose of the test substance. Statistically significant reductions compared to controls in body temperature were observed on test day 0 in males and females administered 500 and 2000 mg/kg. A statistically significant reduction compared to control in the mean number of rearing movements was observed in 2000 mg/kg females on test day 0. Males and females in the 2000 mg/kg group had a statistically significant higher incidence compared to control of high posture on test day 0 while in the open field. No other neuro behavioral parameters were affected. A statistically significant reduction in the duration of movement was observed in 2000 mg/kg males and females on test day 0. Total duration of movement was also decreased in males and females at 500 mg/kg (not statistically significant) compared to control values. Statistically significant reductions in the mean duration of movement were observed in 100 mg/kg females during the 1st and 2nd intervals. Statistically significant reductions in the number of movements were observed in 500 and 2000 mg/kg males and females on test day 0.

Sincerely,